A New era of GDMT: Are we witnessing a convergence of GDMT for heart failure and CKD?

Dr Brendon Neuen
MBBS MSc PhD FRACP FASN
Staff Specialist Nephrologist & Director, Kidney Trials | Royal North Shore Hospital
Senior Research Fellow | The George Institute for Global Health
DISCLOSURES

• Consultancy: AstraZeneca, Alexion, Bayer, Boehringer & Ingelheim, Cambridge Healthcare Research, Novo Nordisk, Traveré Therapeutics, Dedham Group

• Speaker honoraria: AstraZeneca, Boehringer & Ingelheim, Cornerstone Medical Education, The Limbic, Medscape, American Diabetes Association, Renal Society of Australasia

• Trial/consortium steering committees: SMART-C, AstraZeneca, Bayer, CSL Behring

• Grants: National Health and Medical Research Council, Medical Research Future Fund, Ramaciotti Foundation (all Australian)

All honoraria paid to my institution
ARE WE WITNESSING A CONVERGENCE OF GDMT FOR HEART FAILURE AND CKD?

Yes and no...
Key elements of GDMT are shared across heart failure and CKD

T2D & CKD

“Quadruple Therapy”

- ACEi/ARB
- SGLT2 inhibitor
- Non-steroidal MRA
- GLP-1RA

HFrEF & HFmrEF

“Quadruple Therapy”

- ACEi/ARB/ARNI
- β-blocker
- Steroidal MRA
- SGLT2 inhibitor
GDMT FOR ONE CONDITION CAN DELAY OR PREVENT ONSET OF THE OTHER

Heart Failure

ACEi/ARB, non-steroidal MRAs, and SGLT2i prevent HF events in CKD

Chronic Kidney Disease

ARNI and SGLT2i slow kidney disease progression in HF
SGLT2i AND NS-MRA REDUCE HF IN CKD

NDPH Renal Studies Group & SMART-C The Lancet 2022

Filippatos G et al. JACC HF 2022
ARNI & SGLT2i attenuate GFR decline in HF

PARADIGM-HF & PARAGON-HF
McCausland FR et al. Eur J Heart Fail 2022

DAPA-HF
Jhund P et al. Circulation 2021
Newer components of GDMT can enhance the tolerability of RAS blockade and MRA

Heart Failure

- SGLT2i may enable persistent MRA use in HF
- ARNI may enable persistent MRA use in HF

Chronic Kidney Disease

- SGLT2i enables persistent use of RASi in CKD
- SGLT2i may enable persistent use of ns-MRA in CKD
- SGLT2i may facilitate safer use of ETA-RA in CKD
**SGLT2i REDUCES HYPERKALEMIA (K>6.0 MMOL/L)**

### Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>SGLT2i Years</th>
<th>Placebo Years</th>
<th>SGLT2i Events</th>
<th>Placebo Events</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>137/5795</td>
<td>85/4347</td>
<td>8.2</td>
<td>9.2</td>
<td>0.89 [0.67, 1.17]</td>
</tr>
<tr>
<td>CREDENCE</td>
<td>121/2202</td>
<td>154/2199</td>
<td>21.6</td>
<td>27.9</td>
<td>0.77 [0.61, 0.98]</td>
</tr>
<tr>
<td>DAPA-CKD†</td>
<td>159/1455</td>
<td>179/1451</td>
<td>56.9</td>
<td>65.3</td>
<td>0.88 [0.71, 1.09]</td>
</tr>
<tr>
<td>DAPA-HF‡</td>
<td>36/2364</td>
<td>51/2364</td>
<td>11</td>
<td>16</td>
<td>0.64 [0.42, 0.99]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>53/8582</td>
<td>78/8578</td>
<td>1.6</td>
<td>2.3</td>
<td>0.67 [0.47, 0.95]</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>216/4687</td>
<td>124/2333</td>
<td>17.2</td>
<td>20.5</td>
<td>0.83 [0.67, 1.04]</td>
</tr>
<tr>
<td>EMPEROR-Reduced‡</td>
<td>42/1811</td>
<td>57/1824</td>
<td>22</td>
<td>30</td>
<td>0.70 [0.47, 1.04]</td>
</tr>
<tr>
<td>VERTIS-CV</td>
<td>291/5493</td>
<td>157/2745</td>
<td>18.7</td>
<td>21.2</td>
<td>0.90 [0.74, 1.09]</td>
</tr>
</tbody>
</table>

**Overall [p<0.001]**

\[ I^2=0\%, \text{ P-heterogeneity}=0.65 \]

Hazard Ratio with 95% CI: 0.82 [0.75, 0.90]

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**Neuen BL et al. Circulation 2022**
**SGLT2i reduces AKI and Hospitalisations**

**Acute kidney injury**

**SMART-C**

<table>
<thead>
<tr>
<th>Events/participants</th>
<th>SGLT2i</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIABETES</td>
<td>766/40669</td>
<td>856/34090</td>
<td>0.79 (0.72, 0.88)</td>
</tr>
<tr>
<td>NO DIABETES</td>
<td>155/7789</td>
<td>233/7811</td>
<td>0.66 (0.54, 0.81)</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td>918/48458</td>
<td>1092/41901</td>
<td>0.77 (0.70, 0.84)</td>
</tr>
</tbody>
</table>

**Heterogeneity by diabetes status: p=0.12**

**EMPA-KIDNEY: All-cause hospitalization**

**NDPH Renal Studies Group & SMART-C The Lancet 2022**

Preiss D et al. AHA 2022
Effect of SGLT2 inhibitors on discontinuation of RAS blockade: A joint analysis of the CREDENCE and DAPA-CKD trials

**METHODS**

- Two randomized, double-blind, placebo-controlled trials
- 8483 participants
- Temporary (≥4 weeks) or permanent discontinuation of ACEi or ARB

**OUTCOME**

<table>
<thead>
<tr>
<th>SGLT2 inhibitor</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0 per 100 patient years</td>
<td>4.7 per 100 patient years</td>
</tr>
</tbody>
</table>

Consistent effect across:

- GFR
- RAS blockade dose
- Serum K+

More pronounced effect:

- UACR ≥1000 mg/g
- P-interaction=0.01

**Conclusion**

In patients with albuminuric CKD, SGLT2 inhibitors facilitate persistent use of RAS blockade.

Fletcher RA... Neuen BL
J Am Soc Nephrol 2023
doi:10.1681/ASN.00000000000000248
SGLT2i reduces MRA discontinuation in HFrEF

Ferreira et al. JACC 2022
INCIDENCE OF HYPERKALEMIA LOWER WITH ARNI VS. ACEI IN HFrEF

Desai AS et al. JACC HF 2022
ARNI REDUCES MRA DISCONTINUATION IN HFREF

Bhatt AS et al. Eur J Heart Fail 2022
SGLT2i REDUCES DIURETIC INITIATION/INTENSIFICATION IN CKD & HF

**DELIVER**

New Loop Diuretic Initiations Among Baseline Non-Users

- Placebo
- Dapagliflozin

n=1,450

HR 0.68; 95%CI: 0.55 to 0.84, p<0.001

Chatur S et al. Circulation 2023

**CANVAS/CREDENCE**

Oral Diuretic Intensification

- Placebo
- Canagliflozin

HR 0.59; 95%CI: 0.53-0.66

Chatur S… Neuen BL (unpublished)
New insights from SONAR indicate adding sodium glucose co-transporter 2 inhibitors to an endothelin receptor antagonist mitigates fluid retention and enhances albuminuria reduction.

**Selection and matching**

<table>
<thead>
<tr>
<th>Matched Case Control</th>
<th>Atrasantan and SGLT2i (N=14)</th>
<th>Atrasantan (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66 (28.6)</td>
<td>65 (31.0)</td>
</tr>
<tr>
<td>Female sex, n/%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>142</td>
<td>143</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>UACR, mg/g</td>
<td>465</td>
<td>632</td>
</tr>
<tr>
<td>BNP, pg/ml</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>Diuretics, n/%</td>
<td>13 (92.9)</td>
<td>38 (90.5)</td>
</tr>
</tbody>
</table>

**Results**

- **Body weight**
  - Atrasantan and SGLT2i: 1.2 kg
  - Atrasantan: 27.6%

**CONCLUSION:**

Six-weeks combined SGLT2i/atrasantan treatment versus atrasantan alone decreased albuminuria and body weight supporting future studies to characterize the long-term efficacy and safety of combined SGLT2i/ERA treatment.

Heerspink H.J.L. et al, 2020
CONTEMPORARY KIDNEY GDMT IN 2024

Diabetic Kidney Disease
- RASi
- SGLT2i
- ns-MRA
- GLP-1 RA

Non-Diabetic Kidney Disease
- RASi
- SGLT2i
- Ns-MRA
- ETA-RA

Disease Specific Targeted Therapies

Comprehensive Lifestyle Modification

Additive Benefits
- Addressing multiple disease mechanisms

Larger anticipated improvements in albuminuria and eGFR decline
- Enhanced cardioprotection

Enhanced Tolerability
- SGLT2 + RASi
  Hospitalisation, AKI, hyperkalaemia

- SGLT2 + ns-MRA
  Hyperkalaemia

- SGLT2 + ETA-RA
  Diuretic initiation or intensification

Neuen BL et al. (under review)
4 PILLARS OF GDMT IN DIABETES & CKD

- **Outcomes:**
  - CKD
  - MRA
  - All-cause

- **HR (95% CI):**
  - CKD: 0.42 (0.31, 0.56)
  - MRA: 0.54 (0.42, 0.70)
  - All-cause: 0.66 (0.53, 0.83)

- **Favors:**
  - Combination therapy
  - Conventional care

Neuen BL et al. Circulation 2024
Projected mean event-free survival

- Conventional care: 23.7 years (21.4-24.1)
- Combination therapy: 26.9 years (26.1-27.6)

Difference: 3.2 years (2.4-4.0)

Heart failure event-free survival (%)

Neuen BL et al. Circulation 2024
Heart failure event-free survival with combination GDMT in diabetes & CKD

Projected mean event-free survival:
- Conventional care: 19.4 years (17.5-20.8)
- Combination therapy: 24.9 years (23.4-26.1)
- Difference: 5.5 years (4.0-6.7)

Neuen BL et al. Circulation 2024
HEART FAILURE EVENT-FREE SURVIVAL WITH COMBINATION GDMT IN HFREF

Vaduganathan M et al. The Lancet 2020
THEORETICAL APPROACHES TO IMPLEMENTING THE “4 PILLARS” IN CKD

TRADITIONAL APPROACH
RAS blockade, add SGLT2i, re-assess in 3-6 months, add ns-MRA, consider GLP-1 RA
Limitations: Ignores excess early cardiovascular risk, very high risk of therapeutic inertia

RAPID SEQUENCE APPROACH
Rapid sequence implementation of “kidney GDMT”
Considerations: Assumes all patients with CKD are at equally high-risk, cost-effectiveness uncertain, and safety largely untested

ACCELERATED RISK-BASED APPROACH
Identify patients at highest risk using validated risk score, prioritise accelerated implementation of combination guideline directed medical therapy
Appeal: Match intensity of treatment to risk, prioritise patients likely to obtain greatest absolute benefits

Neuen BL, Tuttle KR & Vaduganathan M. Circulation 2024 (in press)
RATIONALE FOR UP FRONT COMBINATION THERAPY: CREDENCE

Many individuals will need combination therapy. Excess early risk is predominantly due to CVD.

Events within first 12 months of CREDENCE:
- Hospitalisation for heart failure or CV death: 120
- Kidney failure: 29
MATCH INTENSITY OF GDMT TO RISK

Accelerated risk-based implementation of guideline directed combination therapy for type 2 diabetes and CKD

Stratify risk using validated risk score (e.g. KDIGO heat map or KFRE)

Very high/high risk
- Early nephrology referral
- Up-front, accelerated sequence combination therapy

Moderate/low risk
- Primary care management
- As needed specialist referral
- Traditional, sequential add-on therapy

Neuen BL, Tuttle KR & Vaduganathan M. Circulation 2024 (in press)
**Risk-based approach: accelerated implementation for those at highest risk**

Concept: Use validated risk score to identify which patients gain greatest absolute benefits accelerated uptake of kidney GDMT

Neuen BL et al. Am J Kidney Dis 2021
**TIMING AND SEQUENCING OF KIDNEY GDMT (AND HF)**

### Traditional/conservative approach
- 2 months
- 3-6 months
- 3-6 months
- 2-3 months

<table>
<thead>
<tr>
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<th>Phase</th>
<th>Action</th>
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<tr>
<td>ACEi/ARB</td>
<td></td>
<td>Titrate dose</td>
</tr>
<tr>
<td>SGLT2i</td>
<td></td>
<td>Re-evaluate albuminuria</td>
</tr>
<tr>
<td>ns-MRA</td>
<td></td>
<td>Titratedose and re-evaluate albuminuria</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td></td>
<td>Up titrate dose</td>
</tr>
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### Accelerated approach
- 2 months
- 2 months
- 2 months

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### Rapid sequence approach
- 2 months
- 2 months

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<td>GLP-1 RA</td>
</tr>
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</table>

*It can take up over 12 months until guideline directed medical therapy for type 2 diabetes and CKD is fully implemented*
Prescribe appropriate protective agents, and follow up

Appropriate knowledge of data
Requirements For Full Utilisation of Proven Therapies

System

Access to health care

Afford health care

Attends for health care

Suitable infrastructure, training and guidelines available

Provider

Prescribe appropriate protective agents, and follow up

Appropriate knowledge of data

Make diagnosis

Undertake appropriate tests- diabetes and/or CKD

Patient

Fill scripts

Take prescribed therapy

Attend ongoing medical care

Continue therapy

Kim D, Perkovic V, Kotwal S. KI Reports 2024
ARE WE WITNESSING A CONVERGENCE OF GDMT FOR HF AND CKD?

Yes:
- Key elements of GDMT are shared across heart failure and CKD
- GDMT for one condition can delay or prevent the onset of the other
- Newer components of GDMT can enable better use of RASi & MRA in both conditions
- Common unanswered questions about timing and sequencing
- Common implementation challenges

No:
- Greater heterogeneity in risk of CKD progression
- Unique treatment considerations in CKD (e.g. negative acute effects on GFR)
- Not all future components of CKD GDMT likely to reduce HF risk (e.g. ETA-RA)
- Need for disease-specific, targeted therapies for non-diabetic CKD (e.g. GNs)